THE EARLY RECOGNITION OF POST-OPERATIVE VENOUS THROMBOSIS*

Increased Prothrombin Activity As An Aid To Diagnosis

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THE problem of venous thrombosis in the post-operative patient or in any patient who is confined to bed, has always been a challenge to the clinician and in spite of extensive laboratory and clinical study, it still presents many unanswered problems. The dramatic and often fatal complication of pulmonary embolism has justifiably received the greatest amount of attention, but the problem of the chronically swollen extremity and the post-phlebitic ulcer are equally perplexing. During the past decade, there have been rapid advances both in our understanding of the basic pathology and in methods of therapy, but the true etiology of the condition is unknown and there is no reliable means of predicting which individuals are liable to develop thrombosis and its complications. There is heated discussion between the advocates of proximal vein interruption and those who champion anticoagulant therapy, but if these two methods of therapy are to stand the test of time, there must be individualization of each patient and in many instances, one method should complement the other. There is great need for some laboratory or clinical method by which thrombosis can be predicted in the individual patient.

Our understanding of the manner in which venous thrombosis develops has been modified as a result of extensive investigation of the post-operative patient and of the conditions found at autopsy. The source of pulmonary emboli has been considered in the past to be almost entirely the thrombi formed about the site of an operation or in the small pelvic veins of the prostatic or ovarian plexuses. Small emboli

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undoubtedly do arise from these sources, but they are probably not the origin of large emboli or the massive fatal embolus. It is now believed that the veins of the leg are the more common source of emboli and that the most dangerous type of thrombus is that which develops in the small veins of the plantar aspect of the foot or in the calf and propagates proximally into the large veins of the legs without causing the typical signs of venous thrombosis. Homans[1] in 1934 suggested that bland thrombosis of the calf veins without inflammatory reaction was the source of multiple pulmonary emboli and was one of the first to perform proximal vein ligation. There is general agreement at present that the leg veins are the most common source of emboli. Denecke, and Olow[2] showed that the earliest symptoms are in the calf and plantar regions. Roessle[3] in 1937 and Neumann[4] in 1938 demonstrated in autopsy material that the calf and plantar veins are the common sites of thrombosis.

The modern concept of the pathogenesis of venous thrombosis differs from earlier opinions on the subject. In the past, femoral-iliac thrombophlebitis was considered to be the result of infection and thrombosis in the large veins of the thigh and groin with resultant venous obstruction, edema and the signs of phlegmasia alba dolens. This process probably occurs, but the clinical picture of the swollen, painful leg of thrombophlebitis more commonly develops as a result of thrombosis in the small veins of the calf or foot with propagation of the thrombus proximally until the entire femoral vein is occluded by a thrombus (Frykholm,[5] Bauer[6]). In the earliest phase, a coagulation thrombus occurs in the small veins which may give no physical signs or symptoms. This may propagate proximally in the popliteal and superficial femoral vein without being attached to the wall of the vein so that the thrombus is actually waving in the blood stream and may at any time, break free as an embolus. This is the Bland Thrombosis of Homans[7,8] or the Phlebothrombosis of Ochsner and DeBakey.[9] If the process continues, the clot then becomes attached to the vein wall, the tributary veins become occluded by thrombi, and the typical signs of phlebitis become evident. This is probably the sequence of events in a vast majority of the patients with thrombo-embolism but it does not explain all situations. In post-partum sepsis the inflammatory process involves the pelvic veins and there may be extension of the thrombosis proximally to the iliac veins with massive embolism or via the ovarian veins with multiple

septic emboli. Pulmonary emboli in cardiac patients may have their origin from mural thrombi or from vegetations on diseased valves.

The etiology of venous thrombosis in an individual is usually difficult to evaluate but there are many factors which may be of importance, especially in the post-operative patient. The most obvious of these are physical factors which are present in varying degrees and which theoretically result in conditions favoring intravascular coagulation. Peripheral venous stasis, most marked in the lower extremities, is often present. Abdominal distension with compression of the abdominal veins causes stasis of venous blood in the legs and thighs. Decreased thoracic excursion as a result of pain from upper abdominal and thoracic incisions results in a decrease in the thoracic negative pressure which is so important in promoting venous return. Position in bed with the hips and knees flexed causes angulation of veins. Pressure on the veins of the legs and lack of muscular activity increase venous stasis. The dehydration which may occur after operations increases the viscosity of the blood and favors coagulation.

Post-operative infection plays a part in thrombosis and was present in 75 per cent of the cases of embolism reported by Morton and associates.[10] The infection was not necessarily localized at the operative site but appeared to be a factor when involving any part of the body.

The age of the patient is an important consideration in venous thrombosis, and the majority of fatal pulmonary emboli occur in patients over 50 years of age. The condition of the heart is very important, as even in incipient cardiac failure there is peripheral venous congestion with stasis. The cardiac status also has an important bearing on the end results of pulmonary embolism. In patients who had no demonstrable cardiac disease, 41 per cent of pulmonary emboli were nonfatal; whereas, 92 per cent were fatal in patients with cardiac disease, and no patient survived a pulmonary embolus if cardiac decompensation was present.[10] Another factor of importance in the older patient is the condition of the vessels. Atherosclerosis is usually considered to be primarily a disease of arteries, but the veins may also be involved.

When the venous circulation is impaired, the irregular intimal surface of an abnormal vein may act as the eddy point at which a thrombus develops. Peripheral vasospasm may contribute to slowing of the circulation and thrombus formation. Varicose veins with their sluggish flow are a particularly susceptible factor.

There are other factors directly related to the altered physiology of the blood during and after an operation. Waugh[11] has shown that there is decreased coagulation time in the post-operative period. He reported a "Heparin-Dilution" method of determining coagulation time which showed a definite decrease in time usually on the third and fourth post-operative days. We have obtained similar results in our laboratory using his method. Crafoord and Jorpes[12] have noted that a larger dose of heparin is rendered inactive in the blood during the first and second post-operative days than at other times and interpret this as indicating hyper-coagulability of the blood. There may also be some alteration in the platelets after operation. Wright[13] believes that there is an increased adhesiveness of the platelets in the post-operative period with an accompanying rise in platelets. Tocantins[14] has found a decrease in the number of platelets on the first, second and third days after an operation with an increase on the sixth and a maximum level on the tenth day. The increase is most marked after sepsis and splenectomy. Laffont and Sirjean[15] found the platelet count elevated several days before puerperal phlebitis developed. Other changes in the blood such as an increase in fibrinogen, hyperglobulinemia, and increased viscosity may contribute to thrombus formation.

Diagnosis of Post-Operative Thrombosis

The diagnosis of frank thrombophlebitis is usually not at all difficult, and the tender, swollen extremity associated with chills and fever is characteristic. The diagnosis of the early bland thrombosis or phlebothrombosis is much more difficult, and requires careful observation of the patient. An unexplained rise in the pulse and/or the temperature may be the first warning sign and demands careful examination of the legs (Allen et al.[16]). Bauer[6] has called attention to the symptom of restlessness and we have been impressed by this as an early symptom. The patients have a sense of "something being wrong," they are restless and worried. Aching or cramp-like pain in the calf may be the first warning. Examination may reveal tenderness in the calf and pain with dorsiflexion of the foot (Homans), the muscles may be tense or spastic and there may be cyanosis of the foot which is evident in dependency and in some early cases, evidence of vasospasm, i.e., coolness and hydrosis. In the early stage, venography has been of assistance in the diagnosis but venograms are difficult to interpret and the diodrast may be irritating

to the veins. There is a tendency at present to rely more on clinical signs and less on venography in the diagnosis of quiet thrombosis. In spite of the most careful observation, there still remains the patient who has a sudden pulmonary embolus without previous warning of thrombosis. There is urgent need for a clinical or laboratory test to detect incipient thrombosis and it is for this purpose that we wish to present our preliminary studies of prothrombin activity in the post-operative patient.

Our first efforts to find a laboratory test which might be of value in detecting early thrombosis was stimulated by the work of Waugh and Ruddick.[11] They used a heparin dilution method of determining blood coagulation time and found the time was decreased during bed rest, in acute inflammatory conditions, in the presence of hemorrhage, and during the post-operative period. Using this method we have found marked reduction in coagulation time in several post-operative patients who developed thrombosis. The test was unsatisfactory for extensive clinical use as it required 12 cc. of blood for each determination and the end point of coagulation was so difficult to read that interpretation of the results was difficult. A decreased prothrombin time was also noted in those patients who developed thrombosis. The determination of prothrombin activity of the plasma is a much simpler laboratory procedure and it seemed worthwhile to study its alterations in the post-operative patient.

There are conflicting reports in the literature concerning the relation of prothrombin activity to thrombosis. Tuft and Rosenfield[17] concluded from their studies using dilute plasma, that an acceleration of prothrombin time is not suggestive evidence of a tendency to thromboembolism. Hurn, Barker and Mann[18] found that the levels of antithrombin and prothrombin are often outside observed normals in patients having a tendency to thrombosis, but that high and low values are present in about equal numbers. Levy and Conroy[19] found decreased prothrombin times during ether anesthesia with a return to normal within 24 hours after the operation. They used the bedside method of determining prothrombin time. The work of Bancroft and Stanley-Brown[20] gives support to the thought that prothrombin activity may give a clue to thrombosis. They determined the "clotting index" according to the formula—C.I. equals $\frac{\text{Prothrombin} + \text{Fibrinogen}}{\text{Antithrombin}}$. An

index of 1.0 or over indicated a tendency to thrombosis and one of 0.3 or less, a tendency to bleed. In a series of post-operative patients, 65 per cent had a normal clotting index and an uneventful convalescence. Thirty-five per cent had a high index and although no frank signs of phlebitis developed, this group all had fever and a prolonged convalescence without any demonstrable cause. Patients with phlebitis all had high indices as did seven patients with pulmonary emboli. They studied patients pre-operatively and on the seventh and ninth post-operative days, and believed that a high index indicated a tendency to thrombosis. Shapiro[21] found a hyperprothrombinemia in patients who had venous thrombosis or a pulmonary embolus. He determined prothrombin time on diluted (12.5 per cent) plasma as well as on whole plasma and found the most consistent decrease in the dilute plasma determination. His results using whole plasma were variable and at times he found a decreased prothrombin activity when thrombosis was actually present. He concluded that a decreased prothrombin time found with dilute plasma was an aid in the differential diagnosis of thrombosis.

Method

Our method of study has been as follows:—Prothrombin activity is determined pre-operatively (the morning of operation) and in the evening after operation. Daily determinations are made each day through the sixth post-operative day. This procedure was followed in a series of 68 surgical patients and 122 obstetrical patients. The initial results indicated that values on the third post-operative day were most significant, and a large series is now being studied doing determinations on the first and third post-operative days. The method used for determining prothrombin activity is as follows and is essentially that described by Quick.[22]

1. *Preparation of thromboplastin:* A fresh human brain is stripped of vessels, gross blood washed off with normal saline, and the tissue macerated by beating at medium speed in an electric mixer. Water and lipids are extracted with large volumes of acetone at low temperature; usually four changes of acetone are required. The granular mass is then placed in a vacuum desiccator and the acetone removed by oil suction pump. The dry powder is kept in a desiccator under refrigeration. For use, 0.3 gm. of the dried powder is suspended in 10 cc. normal saline and the mixture digested at 50-55° C. for 20 minutes with frequent

shaking. It is then centrifuged at 1500 RPM for 5 minutes and the turbid supernatant fluid pipetted off. This is mixed with equal parts of .024 M calcium chloride solution and the mixture placed in a water bath at 37° C. just prior to use.

2. *Standardization of thromboplastin:* Determinations are run in quadruplicate on two fresh plasma samples from each of five normal individuals. Dilutions of 5, 10, 15, 20, 25, 40, 60 per cent, and whole plasma are used and a curve constructed from the average values. Prothrombin activity of an unknown is calculated from this curve.

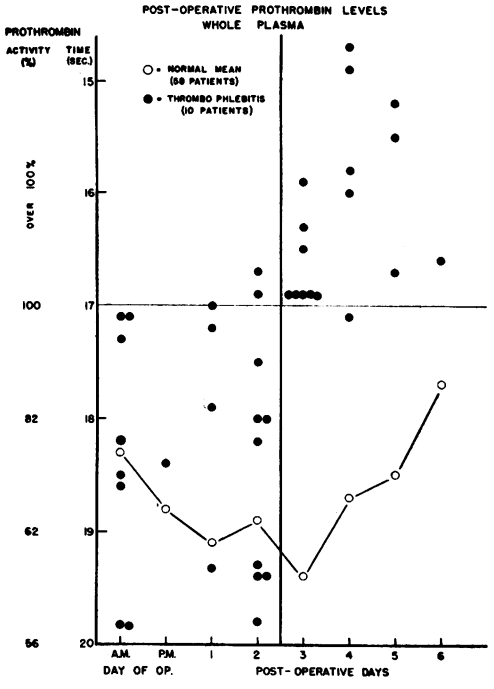
Different individuals may obtain dissimilar results because of differences in reaction time, so they must run checks against each other or carry out separate thromboplastin standardizations. All determinations in this series were done by one individual (R. S.).

3. *Sampling:* Blood is drawn in a dry syringe, avoiding hemostasis as much as possible, and transferred to bottles containing dry oxalate mixture (.006 gm. ammonium oxalate and .004 gm. potassium oxalate in 5 cc. blood). All blood samples in this series were taken by one individual (R. S.) to avoid possibility of error. Hemolyzed or partially clotted blood is not used.

4. *Determination of prothrombin activity:* Blood is centrifuged at 2000 RPM for 10 minutes and the plasma pipetted off. Determinations are run on whole plasma and on plasma diluted to 25 per cent (1:3) with normal saline; 0.1 cc. plasma is pipetted onto a clean watch glass which is placed in the water bath at 37° C. To this is added 0.2 cc. of the thromboplastin-calcium chloride mixture; at this moment the stop watch is started. The mixture is stirred constantly with a glass stirring rod; the end point is reached when clot formation is first observed. A black background facilitates observation of the end point. Determinations are run in triplicate.

Observations

The prothrombin activity of the plasma has been determined in 68 post-operative patients. In 10 of these patients thrombosis developed, and the remaining 58 had no complications. Most of the patients selected were over 50 years of age undergoing major abdominal or chest surgery, or having a history of previous thrombophlebitis. Graph I shows the mean of prothrombin activity in the 58 post-operative patients who did not develop thrombosis. Following operation the pro-



GRAPH I

Hyperprothrombinemia in 10 patients who subsequently developed venous thrombosis. Black dots represent single prothrombin determinations.

thrombin activity decreases (prothrombin time increases) during the first three days and the lowest level usually occurs on the third day. After the third day the level increases and returns to normal about the sixth day. Young individuals have a more rapid return to the pre-operative level—usually by the third or fourth day—and the curves are more variable. Only the average levels of prothrombin activity of whole plasma are plotted on the graph but Table I records the average prothrombin times of both whole and dilute plasma and their statistical variations. There is less variation in the results obtained with whole plasma than with dilute plasma.

The prothrombin activity of whole plasma in patients who developed thrombosis is also shown in Graph I. The ten patients did not

TABLE I

POST-OPERATIVE PROTHROMBIN LEVELS
58 NORMAL PATIENTS

	No. of Patients		*Mean*		*Standard Deviation*		*Coeff. of Variation*	
Dilution	100%	25%	100%	25%	100%	25%	100%	25%
Pre-op (A.M.)	56	50	18.3	33.2	1.25	2.82	.07	.08
Post-op (P.M.)	20	13	19.0	36.7	1.78	2.31	.09	.06
Post-op I	27	21	19.1	35.4	1.27	3.94	.07	0.11
Post-op II	32	26	18.9	33.7	1.31	2.58	.07	.08
Post-op III	17	12	19.4	33.3	1.31	2.20	.07	.07
Post-op IV	24	19	18.7	32.0	1.27	2.43	.07	.08
Post-op V	15	12	18.5	33.9	1.79	3.46	0.10	0.10
Post-op VI	8	7	17.7	31.5	1.71	2.27	0.10	.08

Whole Plasma 17.0 sec. equals 100% activity
Dilute Plasma 29.2 sec. equals 100% activity

all have determinations every day but it is evident that their prothrombin activity varied much more than the normal values on the first and second days and were in general above normal. All of the patients who developed thrombosis were above 100 per cent on the second and third days—two patients on the second and eight on the third day. The increase in prothrombin activity was usually abrupt and was significantly higher in every instance than the values obtained in normal patients. In this group of ten patients, five were treated with anticoagulants and five were not. In some untreated patients, the prothrombin values remained high after the third day but in many the values return to a normal level even though thrombosis is present. A larger series of patients is being gradually accumulated and the results are similar to this group. It appears that a sudden rise of prothrombin activity on the second or more often, the third day is a significant warning of thrombosis. This increased activity has been helpful in non-surgical patients in whom the diagnosis of early thrombosis has been questionable, but once thrombosis is established, the activity has usually returned to normal levels.

Discussion

It is too early to draw far-reaching conclusions from the data which have been presented but the consistent results obtained permit tentative impressions. The hyper-prothrombinemia which has appeared rather uniformly on the third post-operative day in patients who subsequently developed clinical evidence of thrombosis suggests that at this time the thrombotic process is just beginning in small veins. The increased prothrombin activity appears to be a transitory phenomenon as the prothrombin time in untreated patients is often normal during the clinically recognizable phase of the disease. It is possible that the increased prothrombin activity occurs just before actual clotting begins and is a warning that the stage is being set and changes are occurring in the blood which result in thrombosis. Whether or not thrombosis has actually begun when the change in prothrombin activity occurs, this seems the ideal time for the use of anticoagulant drugs.

This warning of impending thrombosis is non-specific in that it seems to be present whenever a thrombus is forming any place in the vascular system. In several patients, the activity has been over 100 per cent and on the following day, a small thrombus has been palpable in an ankle vein which had been used for intravenous infusion during the operation. A positive test appears to be a warning that the patient should be observed carefully and perhaps that prophylactic anticoagulants should be given. It is impossible as yet to judge the diagnostic importance of the test. In the series of patients studied, no one has developed clinical evidence of thrombosis who did not have a positive test. Two patients have had a sudden rise of prothrombin activity on their third post-operative day without developing clinical evidence of thrombosis. Both patients were under 30 years, one had an appendectomy, the other a herniorrhaphy, and both were out of bed and walking on their first post-operative day. It is possible that the test is less significant in young people as the greatest variations in prothrombin activity occur in this age group. Older individuals have more uniform prothrombin activity curves following operation and the change suggesting thrombosis is more pronounced.

It is of interest that the increased prothrombin activity is more uniformly evident in the whole plasma determination than in the dilute plasma which is a more accurate test. If the condition is only hyper-

prothrombinemia, it should be equally evident in both methods. It is possible that some factor other than prothrombin is involved. This is only conjecture and the exact situation has not been investigated.

Prevention of Thrombo-Embolic Complications

The greatest efforts to prevent thrombosis should be directed toward patients in the older age groups as 80 per cent of the complications occur in patients past forty years of age and 50 per cent occur between fifty and seventy-five years (Ochsner,[23] Stich,[24] Allen[25]). Every effort should be made to prevent venous stasis by encouraging active exercise of the patient while in bed and by early ambulation. Fowler's position on the Gatch frame should not be used as it causes constriction and angulation of the great veins. Abdominal distension should be prevented, and deep breathing should be encouraged. The cardiac status of older patients should be improved as much as possible. The operation should be done with minimal trauma, and anoxemia should be avoided. Of greatest importance is the prevention of shock and dehydration which result in sludge formation and increased viscosity of the blood. The prevention of infection is very important. Peripheral vasospasm is a cause of peripheral venous stasis and cold extremities should be treated with heat or other measures to overcome the spasm.

A great amount of discussion now centers about the use of prophylactic vein interruption or anticoagulants to prevent thrombo-embolism. Advocates of either method have published convincing statistics supporting their particular method and at the present time, it is impossible to form an unbiased opinion as to their relative merits. Allen and his co-workers[16, 25] are the foremost advocates of vein ligation, the Swedish workers (Crafoord, Jorpes and Bauer) have had the most experience with heparin, and Barker[26, 27] exemplifies the advocates of dicumarol. A comparison of published statistics is given in Table II. These results are all from a series of older patients in whom thrombo-embolism is most common and in operations in which the danger is greatest. Whichever method one prefers, no one can deny that great progress is being made.

In spite of these advances in prophylactic treatment, there still remain many problems. Crafoord and Jorpes' experience with prophylactic heparin seems ideal, but heparin is expensive, it must be given parenterally, and the control of dosage is a major problem if all operated

TABLE II

PROPHYLACTIC TREATMENT OF THROMBO-EMBOLISM
Comparison of Vein Ligation and Anticoagulants

Treatment	*Number Patients*	*Thrombosis and Embolism*	*Fatal Embolism*	*Authors*
None	302	11%	2.9%	Craaford &
Heparin	325	0	0	Jorpes
None	832†	3.9%	.07% (6 cases)	Edgar Allen
Dicumarol	832	0.4% (3 cases)	0	et. al.
None	458*	12%	5.7%	Arthur Allen
Vein Ligation	458	1.1% (5 cases)	1 case	

† Estimated Complications—Abdominal Hysterectomy.
* Selected cases—Older Age Group.

patients over forty are to receive it. Dicumarol is not expensive, but its dosage is more difficult to control than heparin and requires a trained technical staff. Vein ligation involves a bilateral surgical procedure and we do not know as yet, the late complications of interruption of the superficial femoral vein. We are very hopeful that continued experience will substantiate our present feeling that a sudden increase in prothrombin activity to above normal on the second or third post-operative day indicates incipient thrombosis. At present, the patients having a positive test are given dicumarol in adequate doses. It would probably be more logical to give heparin until the dicumarol effect is evident. For the advocates of vein ligation, this test should help in selecting the cases for treatment.

There has been considerable interest in the prevention of post-operative thrombosis and many reports have shown an impressive decrease in thrombosis and pulmonary embolism. The success of prophylactic endeavors has been properly attributed to the use of vein ligation or anticoagulants but the importance of careful post-operative care must not be neglected. Whenever a clinician becomes interested in this problem the patients are followed more carefully and more attention is paid to general preventive measures such as hydration, leg exercises, etc., which are important factors in minimizing this complication. Also

the difference between control and treated series will be more striking because of alertness in diagnosing thrombosis. There can be no doubt but that many patients have minor thromboses which are completely missed unless attention is being focused on the problem.

At present no final decision can be made as to the relative merits of vein ligation and anticoagulants in the prophylactic treatment. Results in one series of patients treated by both methods are very similar (Table II). The results obtained with heparin and dicumarol are a little better than with vein interruption and the low incidence of thrombosis and embolism in each group is very impressive. There are certain contraindications to anticoagulant therapy which should be carefully observed. It is contraindicated in hemorrhagic diseases and probably should not be used after operations which have a tendency to post-operative bleeding from a large denuded area such as after prostatectomy, Miles operation, and in some chest cases. Dicumarol should not be used in patients with liver disease. Most important of all, neither heparin nor dicumarol should be used unless laboratory facilities are available to carefully follow the course of therapy. Both of these drugs are satisfactory anticoagulants and are usually started simultaneously—the heparin for its immediate effect until the dicumarol effect is evident.

A great advantage of anticoagulants is their general effect on coagulation and they should be effectual wherever thrombosis exists, whereas vein ligation prevents embolism only from the tributaries of the vein distal to the ligature. Also they prevent propagation of a thrombus into tributary and collateral veins. Prophylactic vein ligation is usually performed bilaterally just distal to the profunda femoris vein and is effectual in preventing embolism because of the high percentage of emboli which have their origin from the veins of the leg. It is a relatively simple procedure which can be performed under local anesthesia with little risk. It does not require laboratory control and most patients can be immediately mobilized. The danger of hemorrhage is not a factor. Against vein ligation are possible late effects of ligating the superficial vein such as edema, development of varices, and ulceration. Only by prolonged observation can this feature be evaluated. Also it is difficult for most surgeons to sacrifice a major vein if definite disease does not exist.

It should be emphasized that our experience with the prothrombin activity as a test of incipient thrombosis is limited and no far-reaching

conclusions are being drawn at present. It is difficult to obtain a large series of test cases and this preliminary report is being made so that others may test its efficacy. The abrupt increase in prothrombin activity has occurred on the third post-operative day and seems to be a warning of thrombosis. It is a transitory situation as prothrombin activity is often normal when thrombosis is clinically present. The change is more consistent when whole plasma rather than dilute plasma is used in the determination of prothrombin time. The dilute plasma determination is a more accurate index of liver function and is used to follow patients being treated with dicumarol. Prothrombin activity is not an index of the extent of thrombosis. The test has not been evaluated in patients confined to bed for long periods because of medical conditions or fractures.

Conclusion

1. Using Quick's one stage method of determining prothrombin activity, we have been able to detect a significant change in the whole plasma of patients who subsequently showed signs of venous thrombosis.

2. This is suggested as a test for the early diagnosis of post-operative thrombosis and as a basis for selecting patients who should receive prophylactic anticoagulant therapy.

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